REMARKS

In view of both the amendments presented above and the following discussion, the Applicants submit that none of the claims now pending in the application is obvious under the provisions of 35 USC § 102. Furthermore, the Applicants also submit that all of these claims now satisfy the requirements of 35 USC § 112. Thus, the Applicants believe that all of these claims are now in allowable form.

If the Examiner believes that there are any unresolved issues in any of the claims now pending in the application, the Examiner is urged to telephone Edward M. Fink, Esq. at (732) 906-5654 so that appropriate arrangements can be made for resolving such issues as expeditiously as possible.

Claims 1-10, 14 and 19-23 are presently in the application. Claims 11-13 and 15-18 stand withdrawn from further consideration.

The final requirement for restriction has been noted.

Claims 1-10 and 14 stand rejected under 35 USC § 112 as failing to comply with the written description requirement. The Examiner contends that the claims include subject matter which was not described in the specification in a manner sufficient to convey to one skilled in the art that Applicants had possession of the claimed invention at the time of its filing. The conclusion is reached that the structural and functional relationship of the claimed genus

of nucleic acids is missing. Additionally, it is urged that the structural relationship between the claimed nucleic acid and their function is missing.

A further conclusion is drawn that the specification fails to teach methodology to obviate the problems encountered in gene therapy and suggests that undue experimentation would be required to use the invention as claimed. This rejection is traversed as follows:

In a sincere attempt to overcome the alleged deficiencies set forth by the Examiner, Applicants have restricted the scope of newly amended claim 1. The term "functional fragment thereof" has been deleted. Although the description does not provide a structural and functional definition of a functional equivalent of a nucleic acid having the sequence from -778 to -422. Clearly, it is of major significance that the scope of protection is not restricted to the exact sequence of this specific region. Accordingly, Applicants wish to advance the argument that one skilled in the art will readily understand that the invention is not limited to the exact sequence of Fig. 1 but that mutants of the sequence are also encompassed as long as they have the capacity to drive carcinoma-selective gene expression. This can be readily tested with undue burden as indicated in the instant specification. Similar to the promoter-deletion studies, fusion contacts can be prepared of an equivalent sequence to be tested and a reporter gene, such as GFP or luciferase (see page 14, line 19 to page 15, line 20 of the specification). The constructs can be readily tested in epithelial and non-epithelial cell line to determine the extent of carcinoma-selectivity (see Fig. 2).

Accordingly, the metes and bounds of the claim can be readily assessed.

A new grouping of method claims has been added to the application and are directed to a method for the preparation of a fusion construct which permits epithelium-selective expression of a gene of interest. The functional equivalents of the -722 to -422 region are specifically included.

A careful review of Applicants' specification reveals that an ample experimental teaching of the preparation of constructs and the subsequent testing for epithelium-selective expression. These new claims, as submitted fall within the elected group I since they specifically relate to the manufacture of the elected products.

The Examiner has also raised an enablement objection with regard to claim 14 which is directed to a medicament. The Examiner's position with regard to this claim is that the medicament contemplated involves gene therapy whereas the description fails to provide specific steps for the therapy. The conclusion reached by the Examiner is that one skilled in the art must then rely on the prior art teachings.

A major problem presented in the art pertaining to gene therapy is that the site of integration of the therapeutic DNA into the genomic DNA of the receiver is difficult to control. This site of integration is highly relevant for the level of expression of the therapeutic

gene. If the integration occurs at the heterochromatic site of the DNA, place where no, or only a few genes are active, the expression might be completely blocked. This regulation is commonly known as the position effect of the integrated DNA. Normally this means that only a few percent of the transgenic cell will express the gene of interest. As demonstrated by the cited references, successful gene therapy based upon common promoters known in the art relies more on luck than on wisdom.

Applicants have disclosed that the expression pattern of EGP-2 promoter driven genes is position effect-dependent. This means that, independent of the site of integration, the EGP-2 promoter driven gene will be active and will produce RNA. The results of the transgenic mice presented in the instant application reveal that in all cases the EPG-2 promoter driven transgene expression is epithelium selective (see page 19, line 28 through page 20 line 19 of the specification). It is evident from the description that epithelial neoplasias can now be effectively targeted with a therapeutic construct, thereby relying upon the teaching of Applicants with regard to the unique EGP-2 promoter and general knowledge regarding formulation and delivery.

The Examiner has also noted the reduced efficacy of gene therapy as a consequence of rejection by the host immune system. It should be noted, however, that the immunity argument is valid only if one introduces foreign cells comprising the therapeutic gene (transgenic modified or even embryonic stem cells). The gene therapy contemplated by Applicants relies upon the application of

DNA based vectors, the cells in the human body produce the transgenes themselves, for example, enzymes that can modify a pro-drug into a drug, or induce cell death by any other mechanism available. Accordingly, the immune response argument is not relevant for the form of gene therapy with naked DNA as disclosed by Applicants.

Applicants direct the Examiner's attention to the fact that the current breadth of the claims is now restricted to the EGP-2 promoter which has unique features which make it uniquely suitable for application in gene therapy, features specifically alluded to in the instant application. The conclusion must then be reached that based upon Applicants' disclosure, one skilled in the art would be taught to produce with minimal effort a medicament comprising a therapeutic expression vector driving expression of any gene of interest by the EGP-2 promoter.

Claims 1, 2, 5 and 7-10 stand rejected under 35 USC § 102(b) as being anticipated by Chen et al.

The Examiner urges that the claims are drawn to a nucleic acid comprising a tissue specific promoter that directs carcinoma selective expression, a nucleic acid comprising the promoter and a nucleic acid of interest, a nucleic acid comprising the promoter and as suicide gene, a vector comprising the nucleic acid, a gene delivery vehicle comprising the nucleic acid and a host cell comprising the nucleic acid.

It is contended that Chen et al disclose a DF3/MUCI promoter that is capable of direct tissue specific

and carcinoma selective expression. It is further noted that Chen et al disclose an adenoviral vector (a delivery vehicle) comprising the promoter and a HSV-tk gene(a nucleic acid of interest and a suicide gene). It is then urged that the patentees further disclose that the vector is transduced into CD 34+ progenitor cells. The conclusion is then reached that Chen et al disclose the claimed invention. This contention is traversed as follows:

Claim 1, as amended, is clearly novel and unobvious with regard to the Chen et al reference which is directed to the DF3/MUC1 promoter. Chen very clearly fails to teach or disclose the EGP-2 promoter and fails to provide any indication pertaining to the advantageous use of the EGP-2 promoter to obtain carcinoma-selective expression patterns. Accordingly, it is urged that the rejection over Chen et al is not applicable and it is urged that it be withdrawn.

Claims 3 and 4 stand rejected under 35 USC § 102(b) as being anticipated by Siemieniako et al.

The Examiner notes that these claims are drawn to a nucleic acid comprising a tissue specific promoter that is able to direct carcinoma selective gene expression and which comprises a nucleic acid from -778 and -422 shown in Figure 1, the nucleic acid being isolated from the human body.

It is further urged that Siemieniako et al disclose a promoter of 17-1A antigen. The promoter comprises -1000 to transcription start site. The nucleic acid molecule shown in the Figure in the instant application

is noted as being 5' region of the gene encoding 17-1A antigen. The Examiner concedes that this reference does not teach the sequence of the promoter but contends that the disclosed sequence comprises the -778 to -422 region and inherently has the same function. The conclusion is then drawn that absent evidence to the contrary, the patentees disclose the claimed invention. This rejection is traversed as follows:

The Examiner has stated that claims 3 and 4 were anticipated because they disclosed the 17-1A antigen promoter sequence which would inherently include the -778 to -422 region as claimed herein. This contention is clearly in error. The Siemieniako et al reference relates to the promoter EGP-1 which is also known as GA733-1. In marked contrast thereto, the instant invention involves promoter sequence EGP-2, also known as GA733-2 (see page 3, line 30 of the specification).

Accordingly, Applicants specifically direct the attention of the Examiner to the fact that EGP-1 and EGP-2 although related are separate and distinct genes.

Further evidence of the distinction over the reference disclosure is apparent. Figure 3 of Siemieniako et al discloses a TATA box and a CAAT box in their promoter sequence. The EGP-2 promoter of the invention does not contain a TATA or CAAT box. This is specifically mentioned in the application at page 5, lines 1-5. It is also evident from studies described in the literature that there are differences between the EGP-1/GA733-1 promoter and the putative EGP-2/GA733-2 promoter. Furthermore, Applicants

are transmitting herewith a letter from Alban J. Linnenbach, Ph.D, dated May 24, 1996, the provider to Siemieniako et al of the antigen gene promoter. Dr. Linnenbach clearly states that Siemieniako et al use the designation 17-1A incorrectly and that the study involves the promoter of GA733-1 EGP-1. Accordingly, it is evident that Siemieniako et al neither disclose nor teach what Applicants are claiming and it is urged that the rejection be withdrawn.

Claims 1-10, 14 and 19-23 are now believed to be in condition for allowance and action to that effect is most earnestly solicited.

Respectfully submitted,

July 15, 2005

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Attachment: letter from Alban J. Linnenbach, Ph.D

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CERTIFICATE OF MAILING under 37 C.F.R. 1.8(a)

I hereby certify that this correspondence is being deposited on **July 18, 2005** with the United States Postal Service as first class mail, with sufficient postage, in an envelope addressed to:

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THE WISTAR INSTITUTE
Giovanni Rovera, M.D., *Director*

5/24/96

Dr. Wim Dokter
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The Netherlands

Dear Dr. Dokter:

Enclosed is the pBluescript subclone GA21726-22RS that contains ~250 bp of the GA733-2 promoter, in addition to exons 1, 2, and 3. pBluescript is a 3 kb plasmid vector from Stratagene; it is resistant to ampicillin at 100 μg/ml. The recombinant has a ~5 kb genomic DNA insert with *EcoRI/SalI* ends. Promoter sequences begin at the *SalI* end. The aliquot is in the form of a lyophilized DNA pellet (15 μg).

In your letter of May 3, 1996, you expressed interest a 1 kb promoter region of GA733-2 used in the Sienieniako and Wiland study. This paper does not describe work on the GA733-2 promoter. They use the designation 17-1A incorrectly. 17-1A is synonymous with GA733-2. In fact, what this report describes the promoter of GA733-1, a gene related to GA733-2 (see Linnenbach, et al. *Proc. Natl. Acad. Sci.* 86:27-31 (1989).

Sincerely,

A. Linnenbach

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